REMARKS

I. STATUS AND AMENDMENTS TO THE CLAIMS

This paper is being filed in response to a non-final official action, in which (a) restriction of the claims was made final and claims 20-24 and 47-61 were withdrawn; (b) claims 2-19, 25-44, and 63 were variously rejected under 35 U.S.C. § 112, second paragraph, for allegedly being indefinite, for reciting use claims, claim informalities, and for reciting allegedly vague terms ("Tomudex (Formula IV)," "a predetermined level indicating toxicity," "predetermined blood plasma level"); (c) claims 1-19, 25-46, and 62-63 were rejected under 35 U.S.C. § 112, first paragraph, for allegedly failing to comply with the written description requirement concerning the genus of enzymes that exhibit carboxypeptidase G activity; (d) claims 1-19, 25-46, and 62-63 were rejected under 35 U.S.C. § 112, first paragraph, for allegedly failing to comply with the enablement requirement concerning compounds other than raltitrexed; (e) claims 25-46 and 62-63 were rejected under 35 U.S.C. § 101 as allegedly failing to recite patent-eligible subject matter for reciting use claims; (f) claims 25-36, 38-46, and 62-63 were rejected under 35 U.S.C. § 102(b) as allegedly anticipated by DeAngelis, et al., *J. Clin. Oncol.*, 14:2145-2149 (1996) ("DeAngelis"); (g) claims 1-10, 19, 25-36, 40-46, and 62-63 were rejected under 35 U.S.C. § 103 for allegedly being unpatentable over DeAngelis, Adamson, et al., *J. Clin. Oncol.*, 9:670-674 (1991) ("Adamson I"); Adamson, et al., *J Clin. Oncol.*, 10:1359-1364 (1992) ("Adamson II"); and Krause et al., *Leukemia and Lymphoma*, 43(11):2139-2143 (2002) ("Krause") in view Clarke, et al., *Clin. Pharmacokinetics*, 39(5):429-443 (2000) ("Clarke"); Kalghatgi, et al., *Enzymes and Drugs*, J. Holcenberg and J. Roberts, eds., Wiley, New York (1981), pp 77-102 ("Kalghatgi"); and Bisset, et al., *J. Med. Chem.*, 35:859-866 (1992) ("Bisset"); and (h) claims 11-18 and 37-39 were rejected under 35 U.S.C. §103 for allegedly being unpatentable over Adamson I, Adamson II, DeAngelis, and Krause in view of Clarke, Kalghatgi, and Bisset and in further view of Widemann.

With this paper, Applicants amend claims 1, 3-11, 14, 16-19, 50-52, and 55-56; cancel claims 2, 12, 13, 15; 20-49, 53, 54, and 57-63 and introduce new claims 64-70. Claim 1 has been amended to recite that the method is directed to combating toxicity in the specific antifolate compound raltitrexed comprising administering the specific carboxypeitdase G enzyme caboxypeptidase G_2 (EC 3.4.22.12). Support for this amendment

can be found in the specification as filed, at, for example, original claim 15 (Tomudex has a generic name of raltitrexed) and original claim 63. Claims 3-11, 14, and 16-19 have been amended to clarify the claim language, to reflect the amendment to claim 1, and/or to delete multiple dependencies.

Withdrawn claim 50 has been amended in a similar fashion as claim 1, to recite that the method is directing to monitoring effectiveness of combating raltitrexed toxicity by contacting carboxypeptidase G_2 and the raltitrexed to cleave raltitrexed and monitoring the cleavage of the raltitrexed. Claims 51, 52, 55, and 56 have been amended to conform with the amendments of claim 50. Applicants submit that the amendment to claim 50 places it and claims dependent thereon in the elected Group I – method of combating toxicity of an antifolate compound. It is requested that claims 50-52 and 55-56 be rejoined in the present application.

New claims 64-70 are directed to a method of combating toxicity caused by raltitrexed by administering raltitrexed, determining a clinical marker of raltitrexed toxicity, and administering carboxypepitase G_2 if the clinical marker indicates toxicity. It is submitted that these claims are within the scope of the elected Group I.

Thus, claims 1, 3-11, 14, 16-19, 50-52, 55, 56, and 64-70 are pending and at issue.

II. SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT

Applicants submit a corrected SB08 indicating the year of publication of the Bloom et al document and request that it be considered by the Patent Office. A second copy of the Bloom publication is also submitted. Applicant further concurrently pay the $180 fee for submission of an IDS after the mailing of a first action on the merits.

III. REJECTIONS OF CLAIMS SHOULD BE WITHDRAWN

A. Rejection of Claims under 112, Second Paragraph, as Indefinite Should be Withdrawn

The rejection of claims 2-19, 25-44, and 63 for reciting a trademark (Tomudex®) is obviated by the amendments presented herein, to recite raltitrexed instead of Tomudex®.

The rejection of claims 5 and 7-19 for reciting an allegedly vague term "predetermined level indicating toxicity" has been obviated by the amendment to claim 5 reciting that the level is a plasma level which indicates toxicity. Furthermore, such a plasma level is exemplified in the specification at page 17, lines 25-29. Thus, a toxic plasma level is well understood or easily determined by the ordinarily skilled artisan.

The rejection of claims 6-19 for reciting a term without proper antecedent basis has been obviated by the amendment to claim 6 to correct this language.

The rejection of claims 25-30, 32-35, 37-35, 37-43, 45-46, and 63 for reciting use claims or other informalities is obviated by their cancelation.

Applicants submit that all rejections under 35 U.S.C. §112, second paragraph, have been addressed by the amendments to the claims presented herein, and these rejection can be withdrawn.

B. Rejection of Claims under 112, First Paragraph, for Alleged Lack of Written Description

The rejection of claims 1-19, 25-46, and 62-63 as allegedly failing to properly describe "an enzyme that has carboxypeptidase G activity" has been obviated by the amendments to the claims presented herein, directing the claims to the specific enzyme carboxypeptidase G_2. Thus, the claims are directed to administering a specific enzyme and not an enzyme as defined solely by its function.

The rejection of claims 1-19, 25-46, and 62-63 as allegedly failing to satisfy the enablement requirement is obviated by Applicants' amendments presented herein,

specifying that the claims are directed to reducing toxicity of raltitrexed and administering carboxypeptidase G_2. The Patent Office, on page 8 of the Office Action, admits that such methods are enabled by Applicants.

Applicants submit that all rejections under 35 U.S.C. §112, first and second paragraphs, have been overcome by amendments presented herein. These rejections can be withdrawn.

C. Rejection of Claims under 101 for Alleged Lack of Patent Subject Matter

Rejection of claims 25-46 and 6-63 under 35 U.S.C. §101 as allegedly recited subject matter that is not patent eligible is moot given Applicants have canceled these claims. This rejection can be withdrawn.

D. Rejection of Claims under 102 for Alleged Anticipation

Rejection of claims 25-36, 38-46, and 62-63 as allegedly anticipated by DeAngelis and of claims 25-46 and 62-63 by Widemann is mooted as Applicants have canceled these claims.

E. Rejection of Claims under 103 as Allegedly Obvious

The Patent Office has rejected claims 1-10, 19, 25-36, 40-46, and 62-63 as unpatentable under 35 U.S.C. §103 over Adamson I, Adamson II, DeAngelis, and Krause in view of Clarke, Kalghatgi, and Bisset; and claims 11-18 and 3-39 in view of the same and in further view of Widemann. Applicants traverse the obviousness rejection and offer the following remarks.

Each of Adamson I, Adamson II, DeAngelis, and Krause relates to the use of carboxypeptidase G_2 for treating methotrexate toxicity. Cleavage of methotrexate by carboxypeptidase G_2 and its use in providing an alternative route of methotrexate elimination is acknowledged to be part of the state of the art at the time of the invention, and is discussed in the patent specification at page 6 line 18 – page 7 line 6. There is nothing in these references to teach or suggest that carboxypeptidase G_2 may be useful for treating toxicity caused by raltitrexed.

Kalghatgi is a general review of folate-degrading enzymes with special emphasis on carboxypeptidase G. Kalghatgi is discussed in the patent application at page 6 lines 18 to 28. As confirmed by the Examiner, Kalghatgi teaches that carboxypeptidase G from different sources exhibits considerable variation in substrate specificity (page 86, paragraph 3). The structure of raltitrexed is quite different from the antifolates studied by Kalghatgi. Raltitrexed does have a C-terminal glutamate residue but the immediately adjacent benzene ring is replaced by the heteroaromatic ring moiety thiophene, which the ordinarily skilled artisan would not understand to be an isosteric replacement.

Furthermore, Springer *et al* (1995), which Applicants submitted in the IDS filed on January 4, 2007 and which is described in the present specification, suggest that modifications to the benzene ring of methotrexate may actually be **detrimental** to carboxypeptidase activity (specification page 7 lines 20-24). The ordinarily skilled artisan would therefore be unable to predict whether raltitrexed would be hydrolyzed by carboxypeptidase G_2 at a sufficient rate to combat toxicity because of the considerable variation in substrate specificity.

Clarke fails to cure the deficiencies of the disclosures of the methotrexate art (i.e., Adamson I, Adamson II, DeAngelis, and Krause) or the Kalghatgi review. Clarke merely discloses that clearance of raltitrexed is significantly reduced in patients with compromised renal function, making these patients more likely to experience severe antiproliferative toxicity (abstract; page 431, paragraph 2). This major drawback of raltitrexed and other antifolate drugs is discussed in the patent specification at page 6 lines 7-16. However, there is nothing in Clarke *et al* to teach or suggest a solution to this problem, namely administration of carboxypeptidase G_2.

Bisset also fails to cure the deficiencies of the methotrexate art and Kalghatgi. Bisset teaches that carboxypeptidase G_2 can be used in a synthetic chemical process to prepare poly-γ-glutamyl conjugates of raltitrexed and other quinazoline antifolates. Bisset provides neither disclosure that administration of carboxypeptidase G_2 can be used to combat the toxicity of raltitrexed in an individual nor any suggestion of such administration.

While Bisset does show that carboxypeptidase G_2 can cleave raltitrexed for synthetic chemistry purposes, it gives no indication of the kinetics of the reaction, merely that the reaction is complete at the 94% level in 1.5-2 hr at 30°C (page 863 left-hand column paragraph 1 and Table 1 on page 861) **in a reaction flask**. This in itself is insufficient evidence and does not teach a skilled person that the enzyme carboxypeptidase G_2 would be capable of exerting a useful effect in a therapeutic context (e.g., **in an individual**, as the pending claims recite).

The **affinity** of the enzyme for the substrate can vary enormously and is a critical feature in combating toxicity. In a synthetic only context (such as in Bisset), a relatively low affinity could result in a useful reaction mechanism. However, in therapeutic terms the reaction could still effectively cease at substrate concentrations that would be toxic in an individual. It was the inventors' work, as expressed in the patent application, that established the kinetics of the reaction between carboxypeptidase G_2 and raltitrexed. The results showed that indeed the enzyme had a high affinity for raltitrexed, 7.8 μM, comparable with that for methotrexate of 8 μM, and would therefore be capable of reducing raltitrexed concentrations to a safe level in a toxic therapeutic situation (Example 1 page 33 and page 6 line 31). The finding that carboxypeptidase G_2 had an essentially identical affinity for a compound containing a thiophene ring in place of a benzene ring was indeed unexpected, and there was no prior substantive evidence for this finding.

Moreover, more than a decade passed after the Bisset publication and Applicants' own filing, and the issue of antifolate toxicity was both well known in the art and of great concern. Yet, until the present invention, no-one had contemplated the use of carboxypeptidase G_2 to cleave raltitrexed to reduce its known toxicity **in an individual receiving raltitrexed**. This is a very clear long felt need, a well recognized secondary consideration indicating the non-obviousness of the present invention.

Widemann is a brief abstract describing a study of carboxypeptidase G_2, thymidine, and leucovorin rescue in cancer patients with **methotrexate**-induced renal dysfunction. The use of carboxypeptidase G_2, thymidine, and leucovorin to rescue cancer patients with methotrexate-induced renal dysfunction is described in the patent specification

at page 4 line 1 to page 7 line 6. There is nothing in Widemann to teach or suggest the use of these agents to combat the toxicity of **raltitrexed**.

It is submitted that no combination of the cited art renders obvious the claimed methods of combating toxicity caused by raltitrexed, and this rejection should be withdrawn.

IV. CONCLUSION

In view of the amendments and arguments presented herein, Applicants submit that the pending application is in condition for allowance. Should the Examiner have any question of form or function, he is urged to contact the undersigned at the number indicated below.

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